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# PRE-APPEAL BRIEF REQUEST FOR REVIEW

| Docket Number (Optional) |
|---|
| 92114.005US1 |

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on May 3, 2010

Signature /Sonja Keenan/

Typed or printed name Sonja Keenan

| Application Number | Filed |
|---|---|
| 10/607,623 | June 27, 2003 |
| **First Named Inventor** | |
| Haim D. Danenberg | |
| **Art Unit** | **Examiner** |
| 1614 | Jagos, Donna A. |

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant/inventor
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 56,390
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

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Telephone number

May 3, 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[x] *Total of 1 forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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|---|---|---|---|
| **Applicant(s):** | **Haim D. Danenberg, et al.** | **Confirmation No.:** | **7907** |
| **Serial No.:** | **10/607,623** | **Group Art Unit:** | **1614** |
| **Filed:** | **June 27, 2003** | **Examiner:** | **Jagoe, Donna A.** |
| **Title:** | **METHOD OF TREATING ACUTE MYOCARDIAL INFARCTION** | | |

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**REMARKS - PRE-APPEAL BRIEF REQUEST FOR REVIEW**

In response to the Final Official Action dated February 4, 2010 for the above-referenced application, applicants hereby submit the following Remarks in support of the Pre-Appeal Brief Request for Review. Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71, and 72 are currently pending. The pending claims have been rejected under 35 U.S.C. §103(a) over Pennanen, et al. ("Effect of Liposomal and Free Bisphosphonates on the IL-1β, IL-6, and TNF-α Secretion from RAW 264 Cells In Vitro," *Pharm. Res.*, 12(6):916-922, 1995) and Hack, et al. (U.S. Patent No. 6,090,777) in view of Ylitalo ("Bisphosphonates and Atherosclerosis," *Gen Pharm.*, 35:287-296, 2002) and Hope, et al. (U.S. Patent No. 6,139,871). Additionally, the pending claims have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting over several claims within copending applications 10/871,488 and 11/190,787. However, these allegedly conflicting claims are currently undergoing prosecution and have not been allowed, therefore applicants assert that the claims of the instant application should be allowed. Favorable reconsideration and allowance of this application is respectfully requested in view of the following pre-appeal brief.

**SUMMARY**

The Examiner has rejected pending claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71, and 72 based on a misunderstanding of the pending claims, cited prior art and a misreading of the Szebeni article (submitted by applicant). A proper understanding of applicants' position demonstrates the following: (1) the pending claims are directed to treatment of an urgent

condition, *i.e.*, a patient having an acute myocardial infarction, (2) the Hack reference describes treatment for an acute condition while the other references describe treatments for chronic diseases and therefore would not be combined and (3) the Szebeni article points out that the Hack reference would not be combined with the other cited art because Hack describes inhibiting the complement system, while Szebeni teaches that the compositions described in the other cited art activate the complement system. In view of the Examiner's mistaken understanding of the claimed invention, the cited art, and the Szebeni article, applicants respectfully submit that the pending claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71, and 72 are allowable.

## BACKGROUND

This application contains claims directed to a method of treating an acute myocardial infarction comprising administering a formulation comprising a cytotoxic or cytostatic agent encapsulated within a suitable carrier of a specific size, wherein the formulation reduces a myocardial zone of infarct. An acute myocardial infarction (AMI) occurs when the blood supply to a part of the heart is interrupted resulting in ischemia or oxygen shortage causing damage and potential death of heart tissue, the area of damage is referred to as the zone of infarct. Also claimed is a formulation that targets phagocytic cells, specifically macrophages and monocytes, for destruction thereby minimizing damage to the zone of infarct. The claimed size of the formulation facilitates targeting phagocytic cells to take up the formulation.

## ARGUMENT

The pending claims have been rejected under 35 U.S.C. §103(a). Applicants respectfully disagree.

First, the Examiner contends that the use of the term "having" in the pending claims indicates that the patient "is in possession of a myocardial infarction, but does not specifically convey that the treatment is *during* the myocardial infarction." The Examiner takes the position that although the claims are directed to a patient "having" an AMI, applicant's arguments are based on claims referencing a patient "during" an AMI. However, the Examiner misses the point. A skilled person understands that a patient having (or "in possession of") a myocardial infarction would possess the physical characteristics of a patient during an AMI. For example, a patient having an AMI experiences an increase in the number of phagocytic cells in the zone of infarct. (*See, e.g.*, published application at ¶4.) The number of phagocytic cells in the zone of infarct

continues to increase in a patient having an AMI for a period of time (*See, e.g.*, published specification at ¶6.) It is this acute activation of phagocytic cells, triggered by the onset of the AMI, that results in the damage at the zone of infarct. (*See, e.g.*, published application at ¶5.) Thus, the physical characteristics of a patient are the same during an AMI as in a patient in possession of an AMI (*i.e.*, having an AMI).

Moreover, the Examiner relies on three references that treat chronic diseases, Pennanen, Hope, and Ylitalo. Pennanen treats a "chronic inflammatory disease" while Hope and Ylitalo are directed to treatments for atherosclerosis, which is also a chronic condition. While it may be true that atherosclerosis *can* lead to having an AMI, *preventing* the AMI by treating the atherosclerosis does not equate to *treating* the AMI once it has begun any more than preventing liver failure by treating the underlying alcoholism equates to treating the liver failure by transplant once it has already occurred. The Examiner then combines these chronic treatment method references with a reference, Hack, that describes the use of a C-1 esterase inhibitor to treat AMI. The Examiner maintains this combination of references because "none of the instant claims specifically recite emergency treatment of a patient during an acute myocardial infarction." Applicants respectfully disagree.

Applicants have consistently asserted that a patient "having" an AMI, as recited in the pending claims, is in an emergency situation. Everything about "having an acute myocardial infarction" is generally understood to be an urgent, potentially life-threatening condition. The skilled person understands that a patient *having* an acute myocardial infarction (as the name recites) is in a dire condition requiring emergency (*i.e.*, acute) care, quite in contrast to the long-term chronic progression of atherosclerosis, which the Examiner relies on. The skilled person would not look to a treatment for a chronic disease for guidance in finding treatments for acute diseases. (*See, e.g.*, response filed May 4, 2007 at pp. 10-11, 13; response filed January 7, 2008 at pp. 13-16; response filed May 1, 2009 at p. 10; response filed Nov. 10, 2009 at p. 11.) Acute diseases require quick and sometimes extreme treatments in contrast with chronic diseases which must be tolerated over long periods of time. Furthermore, as in the alcoholism and liver failure analogy, the site of treatment, or prevention, for the chronic state is different from the site of treatment for the acute one.

A skilled person recognizes that the physical events that occur during an acute disease, such as an AMI, are completely different from those occurring during a chronic disease, such as

atherosclerosis. As set forth in the background section of the published application, an AMI prompts an influx of macrophages, which results in tissue injury beyond that caused by ischemia alone. (*See, e.g.*, published application at ¶¶1-8.) The macrophages secrete cytokines which stimulate fibroblast proliferation and promote myocardial damage. It is the acute activation of the macrophages that expand the zone of infarct in a patient having an AMI. (*See, e.g.*, published application at ¶5.) In contrast, atherosclerosis is a slow-progressive disease which causes a build-up of plaque in the blood vessels. (*See, e.g.*, response filed May 4, 2007, p. 10.) While, over many years atherosclerosis *may* eventually lead to an AMI, once a patient has an AMI it is *far* too late to treat the patient for atherosclerosis. These diseases occur at different times, by different processes, and are mediated by different cells. Thus, a skilled person would not look to treatments for chronic diseases such as atherosclerosis for guidance in identifying treatments for acute diseases such as AMI.

Further, in the response submitted on November 10, 2009, applicants explained that one skilled in the art would also not combine Pennanen, Ylitalo or Hope with the Hack reference because, it is understood in the art that liposomes, such as those allegedly described in Pennanen, Hope and Ylitalo, activate the complement system, as evidenced by the article by Szebeni. (*See* Janos Szebeni, "The Interaction of Liposomes with the Complement System," *Critical Reviews in Therapeutic Drug Carrier Systems*, 15(1):57-88 (1998), submitted herein.) However, the Examiner contends that the teachings of Szebeni do not apply to this combination of prior art because the liposomes in Szebeni are haptenized and therefore are not the same as the liposomes in Pennanen or the instant claims. Applicants respectfully point out that the Examiner has not fully considered the article. The Szebeni article provides a review of the state of the art on liposome-induced activation of the complement system and details studies with both haptenized liposomes and non-haptenized liposomes. In fact, the abstract states that "it has been increasingly recognized that regardless of antigenicity, C activation is an intrinsic property of all charged phospholipid/cholesterol bilayers." (*See*, Szebeni abstract.) The article also contains a summary of a study by Wassef that shows non-haptenized liposomes elicit an antibody-mediated activation of the complement system thereby activating it just as haptenized liposomes. (*See* Szebeni, p. 61.)

Hack describes the use of a C-1 esterase inhibitor to inhibit the complement system as a treatment of acute myocardial infarction (AMI). As evidenced in Szebeni, liposomes (with or

without haptens) activate the complement system. Recognizing the incompatibility of these teachings, the skilled person would not combine the teachings of the Hack reference with Pennanen and/or Hope which describe the use of liposomes to reach the claimed invention. Applicants assert that Hack teaches away from using liposomes to treat AMI because liposomes activate the complement system.

For these reasons, applicants respectfully request that the 35 U.S.C. §103(a) rejection be withdrawn.

## CONCLUSION

Based on the foregoing amendments and remarks, applicants respectfully request allowance of this application over the Final Office Action of February 04, 2010.

## AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Pre-Appeal Brief to Deposit Account No. 50-4387, Order No. 92114.005US1.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-4387, Order No. 92114.005US1.

Respectfully submitted,

Cadwalader, Wickersham & Taft LLP

Dated: May 3, 2010

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